

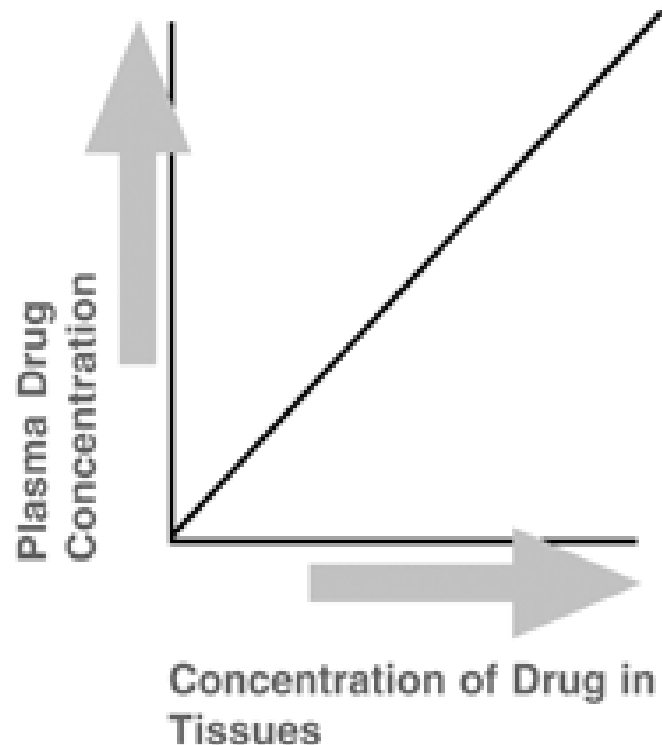
3. Clinical Pharmacokinetics

- **Individualization and optimization of drug therapy**
- **Therapeutic drug monitoring (TDM)**





- Clinical pharmacokinetics: is the process of applying pharmacokinetic principles to determine the dosage regimens of specific drug products for specific patients
 - To the safe and effective therapeutic management of drugs in an individual patient
- Important concepts of pharmacokinetics can serve to characterize the individuality of the patient
- A drug's effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration



- ***Kinetic homogeneity*** - describes the predictable relationship between plasma drug concentration and concentration at the receptor site
- Changes in the plasma drug concentration reflect changes in drug concentrations in other tissues/sites

Figure: Relationship of plasma to tissue concentrations



- For most drugs plasma concentration range (therapeutic range) that is safe and effective in treating specific diseases is **set**.
- But, no absolute boundaries divide sub-therapeutic, therapeutic, and toxic drug concentrations
 - Due to variability in individual patient response, and
 - Variability in fundamental relationship between drug pharmacokinetics and pharmacologic response



- Why for Clinical Pharmacokinetics?
 - Those patients who suffer from chronic ailments such as diabetes and epilepsy may have to take drugs every day for the rest of their lives,
 - At the other extreme are those patients who take a single dose of the drug to relieve an occasional headache,
 - The duration of drug therapy is usually between the extremes.

Individualization and Optimization of drug therapy

1. Dosage regimen adjustment in renal impairment
2. Dosage regimen adjustment in hepatic impairment
3. Dosage regimen adjustment in Pediatrics
4. Dosage regimen adjustment in Geriatrics
5. Dosage regimen adjustment in Obesity
6. Pharmacokinetic drug interactions in combination therapy

Therapeutic Drug Monitoring (TDM)

- TDM, the measurement and interpretation of drug concentration, has been used to individualize drug therapy since the early 1970s
- The aim of TDM is to **optimize** pharmacotherapy by **maximizing** therapeutic efficacy, while minimizing adverse events
- **In those instances where the blood concentration of the drug is a better predictor of the desired effect(s) than the dose**

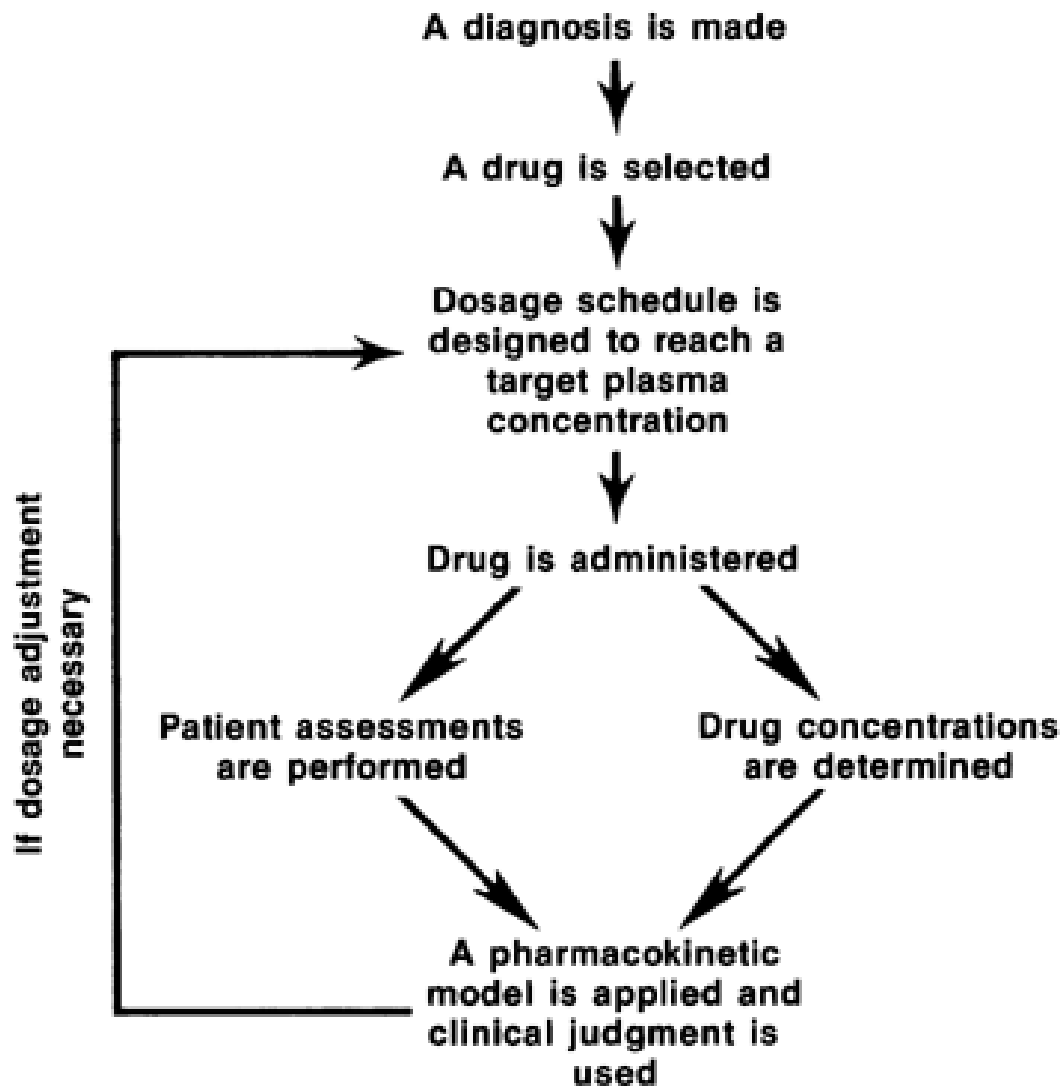


Figure: Process for reaching Dosage decision with TDM



- Clinical pharmacokinetics enables drug regimens to be tailored for individual patients, while minimizing treatment failures and adverse effects.
- Particularly valuable for:
 - Drugs showing a close correlation between **effects** and plasma **concentration**
 - Drugs with a **narrow** margin between toxic and therapeutic effects



- Generally, features of drugs that need clinical monitoring include:
 - Narrow therapeutic range
 - Poor relationship between dose and plasma concentrations
 - Good relationship between plasma concentration and effects
 - Lack of therapeutic effects is dangerous
 - Difficulty in interpreting therapeutic failure



- Drugs that do not need clinical monitoring:
 - Drugs that are used for treating diseases of which their clinical end points can easily be monitored (e.g., BP, cardiac rhythm, blood sugar)
 - Drugs whose serum concentrations show no correlation with therapeutic or toxic effects
 - Drugs with less complicated pharmacokinetics
 - Drugs that are used to treat less complicated or not life threatening diseases



- Generally accepted indications for measuring drug concentrations are as follows:

1. To evaluate concentration-related toxicity:

- Unexpectedly slow drug elimination
- Accidental or purposeful overdose
- Surreptitious drug taking
- Dispensing errors



2. To evaluate lack of therapeutic efficacy:

- Patient noncompliance with prescribed therapy
- Poor drug absorption
- Unexpectedly rapid drug elimination

3. To ensure that the dose regimen is likely to provide effective prophylaxis

4. To use pharmacokinetic principles to guide dose adjustment



- TDM or clinical pharmacokinetic services (CPKS) have been established in many hospitals to evaluate the response of the patient to the recommended dosage regimen
- The improvement in the clinical effectiveness of the drug by TDM may decrease the cost of medical care by preventing untoward adverse drug effects

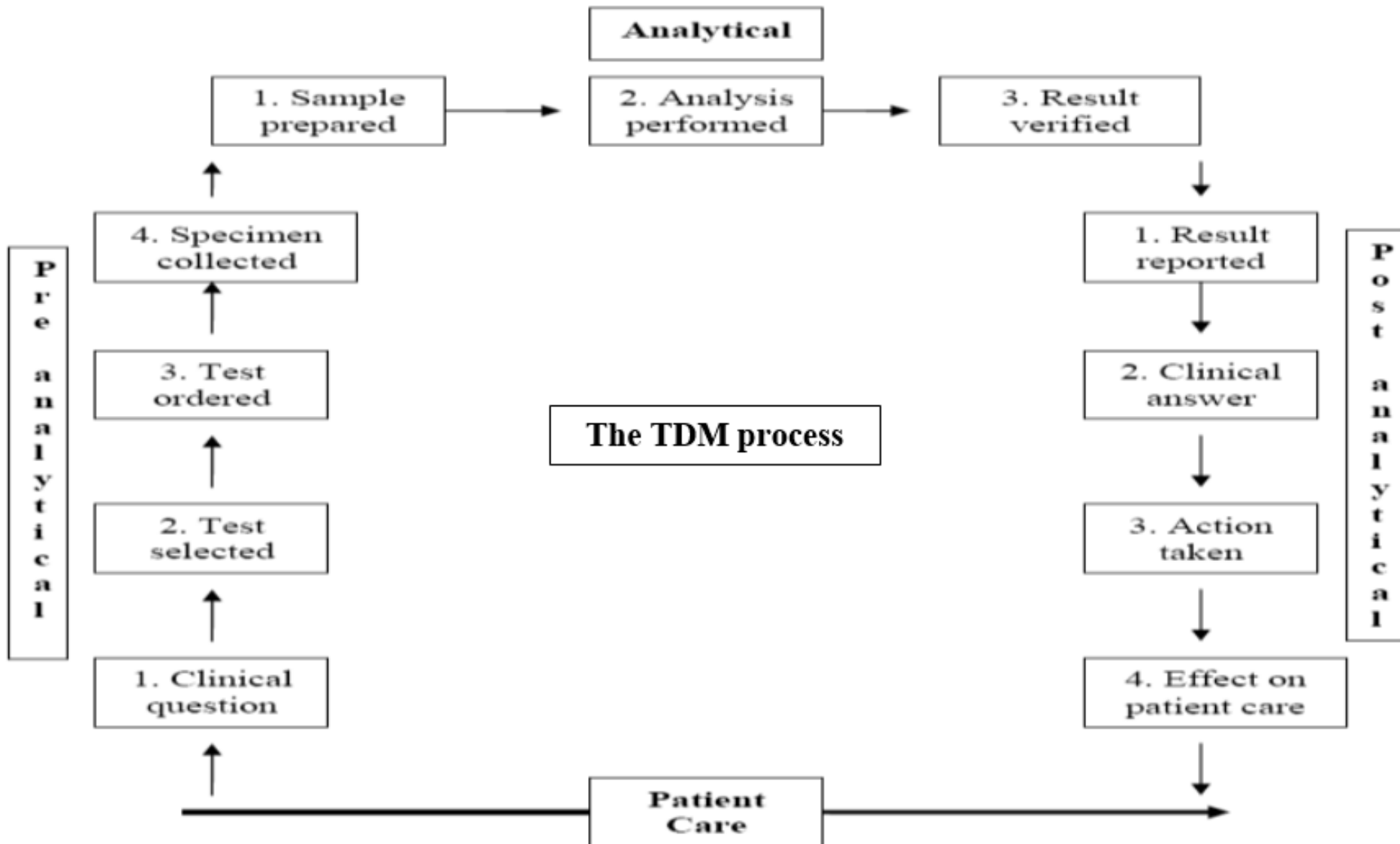


- The functions of a TDM service are:
 - Select drug
 - Design dosage regimen
 - Evaluate patient response
 - Determine need for measuring serum drug concentrations
 - Assay for drug concentration in biological fluids



- Perform pharmacokinetic evaluation of drug concentrations
- Readjust dosage regimen, if necessary
- Monitor serum drug concentrations
- Recommend special requirements

Regulatory Environment





Sample matrices

Venous blood, Serum or Plasma

- Usually drugs are monitored in this matrix
- Whole blood may be used for some drugs like
 - Cyclosporine
 - Tacrolimus
 - Sirolimus and everolimus which distribute between erythrocytes and plasma



Saliva

- It can be used instead of blood in case of infants and children
- It can also be used in the elderly and pregnant women and sometimes in adult patients when venipuncture is difficult
- Easy to collect and preferred by the medical staff as it minimizes their contact to blood samples
- Drugs that can be monitored using saliva are: Phenytoin, Carbamazepine, Theophylline, Digoxin, and lithium
- Drugs of abuse such as morphine and cocaine can also be monitored by saliva



Urine

- Urine as a biological matrix for drug monitoring has many advantages
 - Samples can be easily collected and are well accepted by patients
 - Its window for identifying drug use is broader compared to blood
- Used in TDM service to anticonvulsant and psychoactive drugs



Tears

- Used to a lesser extent
- Due to its pH, only unionized and acidic drugs with high pKa values distribute in tears in a predictable manner
 - Limits its use to small variety of drugs like valproic acid

Hair and nails

- They are used in drug abuse and forensic examination
- Moreover, they can be used in antifungal drugs monitoring



Sweat

- Recently used for determination of drugs of abuse
- Sampling procedure and method of analysis are very complicated

Bile

- Measurement for patients with previously undergone biliary tract surgery
- Drugs: Penicillins, cephalosporins, aminoglycosides, and cardiac glycosides



Feces

- Limited to studies in new drug development and may provide information on excretion of drugs and metabolites

Fetus blood and amniotic fluid

- Used for detecting of drugs that can affect the fetus such as some antibiotics, anticonvulsants and tranquillizers



Breast milk

- Used to determine the amount of drug that can be ingested by the breastfeeding infant
- Phenobarbital, theophylline, and some psychoactive drugs as well as drugs of abuse might be detected in breast milk



CSF

- Necessary to establish if the concentration of a drug in the CNS is desirable for the drug effect or not
- Collection of CSF is not an easy technique since it is done by lumbar puncture
- Examples: antibiotics that are used in CNS infections, anticonvulsants, psychoactive drugs, and protease inhibitors



Bronchial secretions and peritoneal fluid

- Are rarely used
- Used for patients with serious diseases
- Require invasive techniques for sample collection

Seminal fluid

- Drugs like antimicrobials, sulfasalazine, salicylate, propranolol, and protease inhibitors are monitored in the seminal fluid



- Analytical techniques used in TDM:
 - UV Spectrophotometry
 - Gas-Liquid Chromatography (GLC)
 - Radioimmunoassay (RIA) technique
 - An automated, homogeneous Enzyme Immunoassay Techniques (EMIT)
 - Enzyme- Linked Immunosorbent Assay technique (ELISA)
 - High Pressure Liquid Chromatography (HPLC)
 - Turbulent Flow Chromatography (TFC)
 - Fluorescence Polarization Immunoassay (FPIA)



- We will see selected drugs to illustrate the clinical use of PK in improving the prospects for successful drug therapy:
 - Aminoglycosides: Gentamicin
 - Anticonvulsants: Phenytoin
 - Cardiac Glycosides: Digoxin
 - Immunosuppressants: Cyclosporine (Read)
 - Other drugs: Theophylline and Lithium



Aminoglycosides: **Gentamicin**

- Aminoglycosides have concentration-dependent bactericidal activity against Gram-negative aerobic bacteria.
 - The higher the concentration, the more extensive and the faster is the degree of bactericidal effect
 - It has been shown that aminoglycosides eradicate bacteria best when they achieve a $C_{\max}$:MIC ratio of at least 8-10



- AG related toxicity is increased if peak levels are consistently maintained above **12 to 14 µg/ml** or trough levels consistently exceed **2 µg/ml**.
- In addition to variation in bacterial sensitivity which alter the minimum effective concentrations, there is also the difficulty of relating plasma concentration to potential for toxicity.
- Variability exist both in bacterial resistance and patient sensitivity.



Pharmacokinetics (aminoglycosides)

- When given by IV infusion over 30 minutes, aminoglycosides follow a 3-compartment pharmacokinetic model; α (distribution), β (elimination), and γ (tissue release)
 - When infused over one hour, the distribution phase is usually not observed
 - The γ -phase begins approximately 16 hrs post infusion
- Because of complexity of this model, the simpler one compartment model is widely used



- **Absorption**

- AGs have a limited oral bioavailability; must be administered parenterally to treat systemic infections.

- **Distribution**

- AGs are water soluble compounds that rapidly distribute into the ECF and highly perfused tissues, and concentrate in the kidneys.
- Plasma protein binding is negligible (<**20%**)
- The average V_d in healthy adults is **0.26 L/kg** (range: 0.2-0.3 L/kg)



- **Elimination**

- Eliminated **almost entirely** by the kidney via **glomerular filtration**
 - Because of the narrow therapeutic margins of these drugs, dosage should be reduced in patients with renal impairment
- AG elimination is closely correlated with creatinine clearance
- Cystic fibrosis patients, major body burn, ICU patients show increased AG elimination



The need for monitoring

- The narrow therapeutic index,
- Wide patient variability,
- Serum concentration are highly unpredictable,
- The $t_{1/2}$ values show wide inter-subject variation,
- Variations in bacterial sensitivity



Dosage considerations

- The mean values for AG half-lives are generally reported as 2-3 hrs and the volume of distribution as 0.2-0.3 L/kg
 - Influenced by age, disease, and subject to variability
- AGs do not distribute into adipose tissue, but they do enter the ECF. Therefore, correction required for:
 - Obese patients, patients with cystic fibrosis, patients with ascites, and dehydration



- Since AGs are primarily distributed throughout ECF, dosing on a body weight basis may result in overdoses.
- It has been tried to improve this by adjusting the dosage based on **lean body weight**.
- Still this fails to consider the dosing interval which is dependent on both renal clearance and distribution.
- It suggested to use a "corrected creatinine clearance" to account for the fact that a single clearance value may be operating on different V_d values.



- Dosing weight (DW) is normally estimated from the ideal body weight (IBW) and actual body weight (ABW) of the patient:
- Males: $IBW = 50 \text{ kg} + 2.3 \text{ kg for every inch over 5 ft}$
- Females: $IBW = 45.5 \text{ kg} + 2.3 \text{ kg for every inch over 5 ft}$

$$\mathbf{DW = IBW + 0.4(ABW - IBW)}$$

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- The reduced dose during renal insufficiency may be approximated from:

$$\textit{Adjusted dose} \equiv \textit{Dose} \frac{CL_{CR}}{100}$$

where the creatinine clearance, CL_{CR} value in ml/min



- CL_{CR} values may be roughly approximated from creatinine serum concentration C_{CR}

- Males:

$$CL_{CR} \equiv \frac{[140 - age(yr)][wt(kg)]}{72C_{CR}}$$

- Females

$$CL_{CR} \equiv 0.85CL_{CR}(Males)$$



Individualized Dosage

- Since creatinine renal clearance values don't result in reliable dosage adjustments, it has been suggested that the drug itself be used to calibrate the patient
- An initial dose must be administered in order to determine the Gentamicin time course and calculate subsequent doses
- The test dose and subsequent doses are given by constant-rate infusion over a 1hr period and a minimum of three blood samples are analyzed during the post-infusion phase
 - Usually 30min after termination and 1 and 3hr later



Anticonvulsants: Phenytoin

Pharmacokinetics

- Phenytoin exhibits zero-order pharmacokinetics;
- Phenytoin pharmacokinetics are significantly affected by a number of other drugs and metabolites



- **Absorption**

- Phenytoin is a relatively insoluble weak acid, usually administered as the sodium salt
- Particle size is the most important determinant of phenytoin absorption

- **Distribution**

- Phenytoin has a moderately large volume of distribution and is approximately **90%** bound to plasma proteins
- Phenytoin diffuses rapidly into the tissues
- It has a volume of distribution of 0.65 L/kg
- Following IV administration, the distribution phase lasts about 2h



- **Metabolism**

- Phenytoin is **largely** cleared by **hepatic** metabolism
- The metabolism of phenytoin is capacity limited
 - The enzyme system involved is saturable within the therapeutic range of serum concentrations
- This gives rise to a non linear dose-concentration relationship

- **Elimination**

- To achieve therapeutic concentrations, the rate of administration must approach the maximum rate at which Phenytoin can be eliminated
- Saturation elimination kinetics occur within the therapeutic range of serum concentrations



- The free Phenytoin level is the best indicator of adequate therapy
- 10% of Phenytoin circulates in the free, unbound form
 - Phenytoin, Total
 - Therapeutic concentration: 10.0-20.0 µg/mL
 - Toxic concentration: ≥ 30.0 µg/mL
- Clinically important displacement can be caused by bilirubin and several drugs, particularly sodium valproate
 - Displacement will lower the total serum concentration (??)



Pharmacokinetics of Phenytoin in Special Situations

Neonates

- Phenytoin readily crosses the placenta and, maternal and neonatal serum concentrations are roughly equal at birth
- Neonates born to epileptic mothers are able to metabolize phenytoin effectively
- Indeed the short half-lives they show suggests that the fetal liver may have been induced
- However, plasma protein binding of phenytoin is lower in the neonate



Elderly

- Serum phenytoin concentrations for a given daily dose are higher in the elderly than in young adults (??)
- As the serum albumin tends to fall with age, allowance should be made for reduced binding



Pregnancy

- Serum Phenytoin concentrations tend to fall during pregnancy:
 - Increase in V_d during pregnancy,
 - The reduction in serum albumin concentration,
 - The most likely explanation is enhanced hepatic metabolism



Liver Disease

- The binding of Phenytoin to serum proteins is reduced in liver disease.
 - Due to hypo-albuminaemia, displacement by bilirubin or other substances, &/or a change in the configuration of albumin
- This is expected to cause a fall in serum Phenytoin concentration due to an increased fraction of unbound drug available for metabolism
 - But, this may lead to impairment of drug metabolism, which may in turn cause Phenytoin intoxication



Renal Disease

- Uraemic patients have lower serum Phenytoin concentrations than non-uraemic patients:
 - Presence of binding inhibitors
 - An alteration of the albumin molecule
 - Induction of metabolism
 - The concentration of albumin may be reduced in renal disease



- Why Phenytoin be Monitored?
 - Large pharmacokinetic variability
 - Low therapeutic indices
 - Clinical effect not easily quantifiable
 - Generally good correlations between plasma levels and therapeutic effect
 - Saturable metabolism with Phenytoin (Nonlinear)
 - Absorption is variable
 - Drug interactions common

Description for Concentration-dose Relationship

- Michaelis-Menten equation is employed:

$$\frac{dX}{dt} = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

V_{max} = maximum amount of drug that can be metabolized per unit time

K_m = Michaelis-Menten constant, representing the concentration of phenytoin at which the rate of this enzyme-saturable hepatic metabolism is one-half of maximum

C_{ss} = average steady-state phenytoin concentration

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- The above equation can be expressed as*:

$$\frac{X_o}{\tau} (S) = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

X_o/τ = amount of phenytoin free acid divided by dosing interval (which can also be expressed as X_d , meaning daily dose of phenytoin free acid)

S = the salt factor or the fraction of phenytoin free acid in the salt form used

- * The oral bioavailability of phenytoin is considered to be 100%, so an F factor is not needed in these calculations

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- The second equation can then be rearranged to solve for C_{ss} :

$$C_{ss} = \frac{\frac{X_o}{\tau}(S) \times K_m}{V_{max} - \frac{X_o}{\tau}(S)}$$



Individualized Dosage

- Ideally, K_m and D (the maximum dose that can be metabolized) values should be derived for each patient before treatment is begun
- But, in practice this is demanding because multiple serum concentration estimations following administration of a single dose are necessary
- Alternatively, a small dose, say 200mg a day in adults can be started and the steady-state serum concentration measured after 2 to 3 weeks



- From the value obtained, a prediction of the dose adjustment necessary to produce a therapeutic concentration can be made from Phenytoin nomogram
- Development of the nomogram required the assumption that K_m does not vary from one patient to another and this is clearly incorrect
- Once a further steady-state concentration is available on a second dose, more sophisticated methods can be used in which individual Michaelis-Menten parameters are calculated

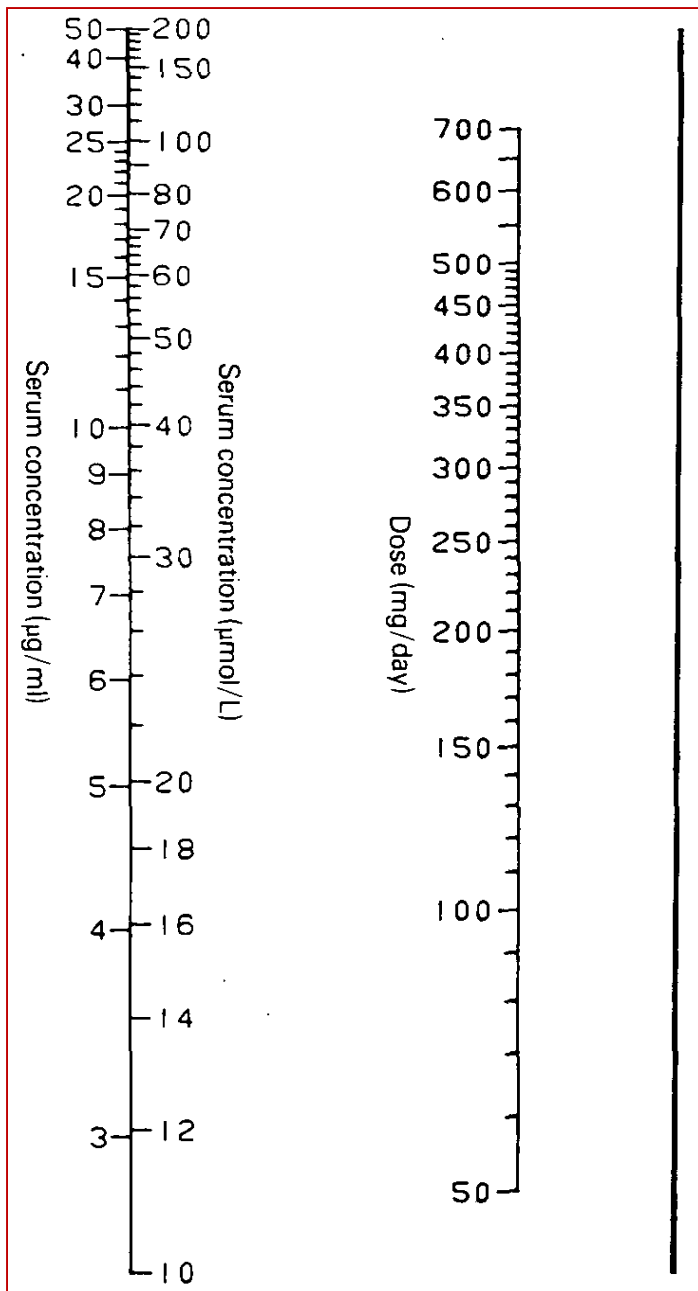


Figure: Phenytoin nomogram

- Given a single reliable serum concentration on a given daily dose of phenytoin, the dose required to achieve a desired serum concentration can be predicted
- A line is drawn connecting the observed serum concentration (left hand scale) with the dose administered (centre scale) and extended to intersect the right hand vertical line. From this point of intersection, another line is drawn back to the desired serum level (left hand scale)
- The dose required to produce this level can be read off the centre scale

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- Rane (1979) points out that body surface area is, in fact, a better guide to dose than body weight (particularly for children)
 - A median dose of phenytoin, the dose/kg of body weight basis, in adults is 300 to 350mg/day (about 5mg/kg)
 - A dose scheme which is approximately proportionate to body surface area is given by:

$$\text{Dose}_{\text{paediatric}} = \text{Dose}_{\text{adult}} \left(\frac{\text{Weight}_{\text{paediatric}}}{\text{Weight}_{\text{adult}}} \right)^{0.7}$$

Dose Intervals and Time to Steady-state

- Because Phenytoin metabolism is saturable, the effective plasma $t_{1/2}$ gradually lengthens as the C_{ss} rises (i.e. the clearance gradually decreases)
- On average, the effective $t_{1/2}$ at very low serum concentrations is about 13hr, but this lengthens to 46hr when the steady-state concentration reaches the C_{max}
- The time to steady-state therefore depends upon the dose and the final concentration reached
- The rate of elimination on discontinuing therapy may be much slower than expected



Cardiac Glycosides: **Digoxin**

Pharmacokinetics

- Following IV injection the serum digoxin concentration time course may be described by a **bi-exponential** equation
- The first exponential is associated with delivery from the blood to the site of action
 - This rapid phase lasts 6-8hr with a half-life of approximately 40min
 - Following this initial distribution, the response has been shown to be correlated with digoxin plasma concentrations

■ **Absorption**

- Absorbed passively in small intestine
- Rate of absorption decreased with meals, but not the extent
- Oral bioavailability (F) ranges from 0.5 - 0.9 (average ~ 0.70)

■ **Distribution**

- Best described by a two-compartment model
- Digoxin does not distribute into adipose tissue

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- $V_d = 7.3 \text{ L/kg}$, is decreased in CRF (4-5 L/kg)
 - V_d is larger in children and neonates
 - Protein binding: 20-30%
 - In patients with severe renal dysfunction, digoxin is only 18% protein bound
 - **Elimination**
 - Major route of elimination is renal; 75-85% excreted unchanged by the kidney
 - Considerable biliary excretion of digoxin is also evident
-

Need for Digoxin monitoring

- Studies show digoxin concentration in serum and in heart muscle to be correlated
- In spite of this correlation, the plasma concentration required for similar responses vary widely between patients
 - Some patients elicit toxic manifestations at low or what are considered therapeutic plasma concentrations; while others show suboptimal responses at what are considered toxic levels
 - An absolute standard for a therapeutic window for the overall population cannot be defined

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- The uncertainty with regard to ideal digoxin plasma levels makes concentration-based predictions unreliable
 - Most patients exhibit a satisfactory inotropic effect at steady-state digoxin levels of **0.7 - 1.5 ng/ml**
 - Monitoring steady-state digoxin levels can be combined with clinical observations to identify patients who are either ultrasensitive or resistant to digoxin
 - Two of the most prominent features of digoxin are its **narrow therapeutic index** and an **endpoint of therapy** which is difficult to define and measure
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- When should Digoxin levels be monitored?
 - When standard doses would not be expected to produce satisfactory effect without toxicity, e.g. renal insufficiency, hypokalaemia, hyper- or hypothyroidism
 - When toxicity is suspected, e.g. anorexia, nausea, vomiting, confusion in the elderly, visual disturbances or arrhythmias
 - When compliance is in doubt
 - When a Digoxin-drug interaction is known or suspected
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Other drugs: **Theophylline**

Pharmacokinetics

- Following IV injection, theophylline blood concentration is described by a two-compartment open model
 - The α -phase (distribution phase) is completed within roughly 30min and is very rapid relative to the β -phase (post-distribution phase)
- For clinical decisions, theophylline may be regarded practically as monoexponential disposition

■ **Absorption**

- Theophylline is quickly and completely absorbed (>90%) from solution and rapidly releasing tablet

■ **Distribution**

- Unlike elimination, distribution and absorption parameters are relatively stable
- 55-63% plasma protein bound
- The apparent V_d is approximately 0.5 L/kg; V_d is relatively constant and displacement from bound protein is insignificant

- **Elimination**

- Show variability
- Diseases that affect liver blood flow, such as cirrhosis and heart failure, may reduce theophylline clearance

Need for Theophylline Monitoring

- Inter-subject variability in biological half-life, despite its linear pharmacokinetics
- In spite of normally linear kinetics, the $t_{1/2}$ varies from **3 to 20.7 hr** in healthy adults and 1.4-7.9hr in asthmatic children
 - This may be attributed to genetic factors, since only 7% of the IV dose is excreted intact in the urine
- Theophylline also has a narrow therapeutic index

Dosage considerations

- Since absorption is rapid and complete, loading dose equation for IV administration;

$$D_L = C \times V_d$$

Can be used without individualization

- But, initial estimation of maintenance dose is dependent on $t_{1/2}$
- Variability in plasma clearance is so great that no constant infusion can be recommended that can reasonably predict both therapeutic efficacy and safety

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- The clearance of theophylline is affected by many variables which necessitate carefully individualized dosage
 - Age, smoking, congestive heart failure, other diseases and drug interactions all contribute to a change in the metabolism of theophylline
 - So wide is the variation in clearance rates that no dose which will produce effective levels of theophylline in most patients will produce toxic levels in a few
 - In patients having no residual theophylline levels prior to therapy, the loading dose may range 5-7.5 mg/kg
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